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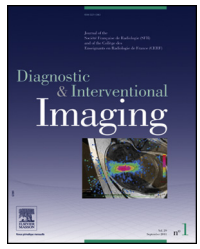

REVIEW / *Breast imaging*

Correlation between imaging and molecular classification of breast cancers

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Abstract The histological type of tumour according to the WHO: ductal, lobular, rare forms, is correlated with specific aspects of the imaging based on each type. This morphological classification was improved by knowledge of the molecular anomalies of breast cancers, resulting in the definition of cancer sub-groups with distinct prognoses and different responses to treatment: luminal A, luminal B, HER2 positive, basal-like, triple-negative. Studies are beginning to deal with the appearance of each sub-type in the imaging. It is now important for the radiologist to be familiar with them.

According to the WHO, the type and histological grade of the tumour are indispensable diagnostic and prognostic morphological elements for the care of breast cancer. The prognostic and predictive elements of the response to treatment are also important, that is, in addition to the histological grade, the hormone receptors (oestrogen receptors [OR] and progesterone [PR] receptors) and the HER2 status. New techniques of molecular biology (''arrays'') now allow for simultaneous analysis, for a single tumour, of the amplification status or deletion of thousands of DNA sequences as well as the level of expression of RNAm of thousands of genes to determine discriminating profiles of chromosome alteration or gene expression. The breast cancers, in particular the infiltrating ductal carcinomas, are thereby reclassified according to the genome alterations underlying very different prognoses: this is the molecular or ''intrinsic'' classification distinguishing the luminal A, luminal B, HER2 positive, basal-like, triple-negative sub-types.

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Genome tests determining a prognostic signature have developed although they do not currently have any clinical application in France. However, correlations between this molecular data and the morphology, the immunohistochemical grade and profile of infiltrating carcinomas have been established.

We propose reviewing the ''classic'' radio-histological aspects of infiltrating carcinomas according to their morphology and then the imaging aspects according to ''traditional'' histoprognostic factors and then describe the new molecular classification that the radiologist should now be familiar with. Although there has recently been a fairly abundant literature in molecular biology and clinical oncology on breast cancers, the same is not true about the correlations between tumour sub-type and imaging. Studies on the literature concerning aspects of the mammography, sonography and MRI are still numerous, retrospective and with different methodologies.

Correlations between imaging and WHO histological types (XXth century)

Initially, the WHO defined breast cancer by its morphological and immunohistochemical characteristics [1].

Infiltrating ductal carcinoma (IDC)

It accounts for 70 to 80% of the infiltrating cancers. Macroscopically, it involves a hard tumour with star-shaped outlines, rarely of soft consistency or with sharp outlines. The histoprognostic grading takes into account the differentiation (formation of tubes or glandular tissue), nuclear atypies and mitoses (counted in the most active zone), determining three grades of malignancy (Figs. 1a, b).

The aspects in the imaging are known: irregular or stellar mass (Fig. 1c), architectural distortion, microcalcifications, rarely round mass.

Infiltrating lobular carcinoma (ILC)

It accounts for 5 to 15% of the infiltrating cancers. Macroscopically it consists of a lesion that is more palpable than visible. The tumoral infiltration often complies with the pre-existing architecture of the breast tissue. The loss of expression of l'E-cadherine, an intercellular adhesion protein (diagnosed in immunohistochemistry by the absence of membrane marking), defines ILC whose cells are no longer cohesive. The cells are small, isolated or in ''Indian file'', surrounding canals or infiltrating the links of the fat tissue without reaction stroma (Figs. 2a, b). This partly accounts for the difficulties in detecting it.

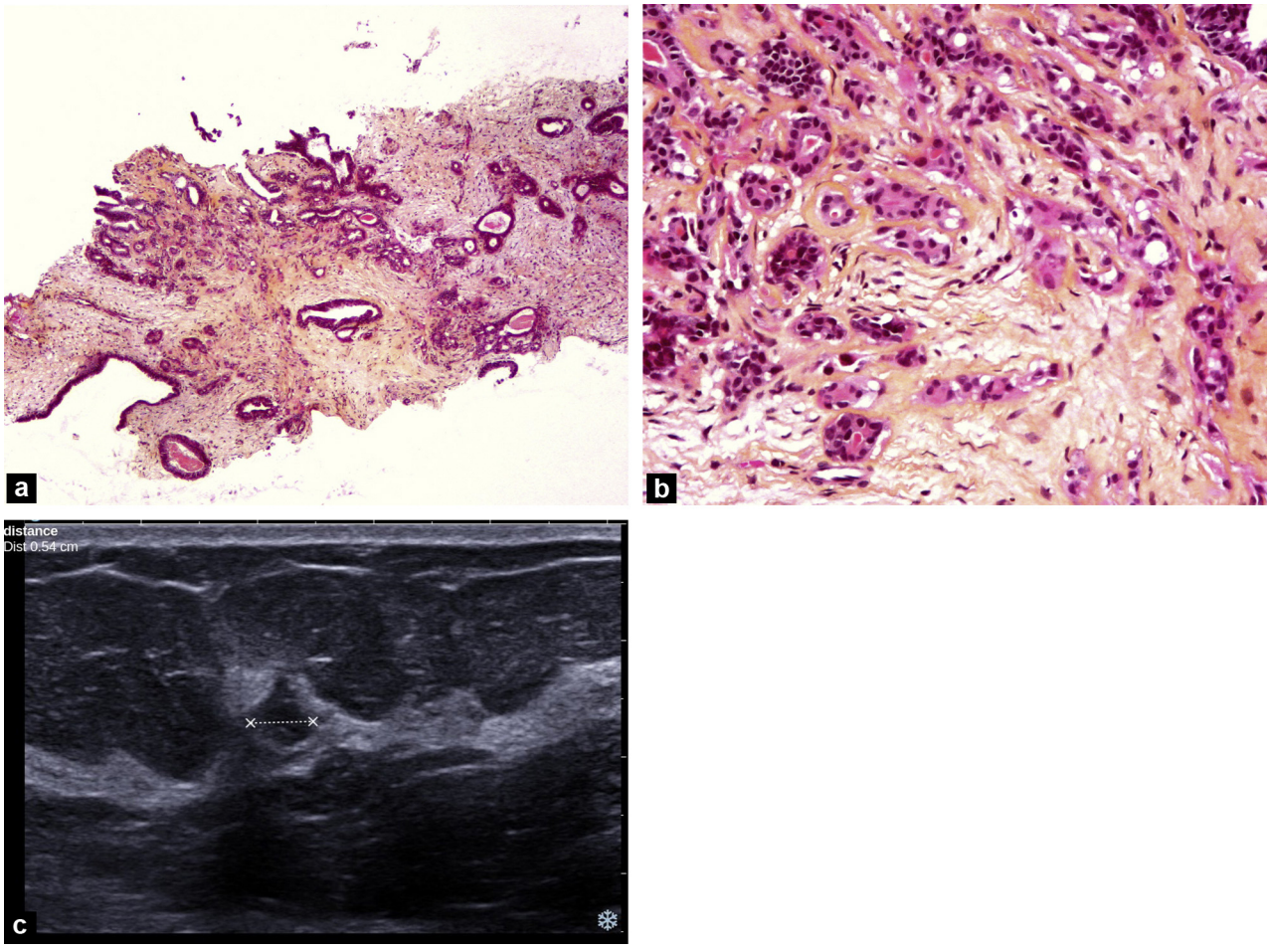

Figure 1. Infiltrating ductal carcinoma. a: core biopsy under sonography: destruction of the normal epithelial structures by a malignant infiltrating proliferation; b: HES × 64. Formation of tubes and framework; c: sonogram: irregular mass of 5 mm.

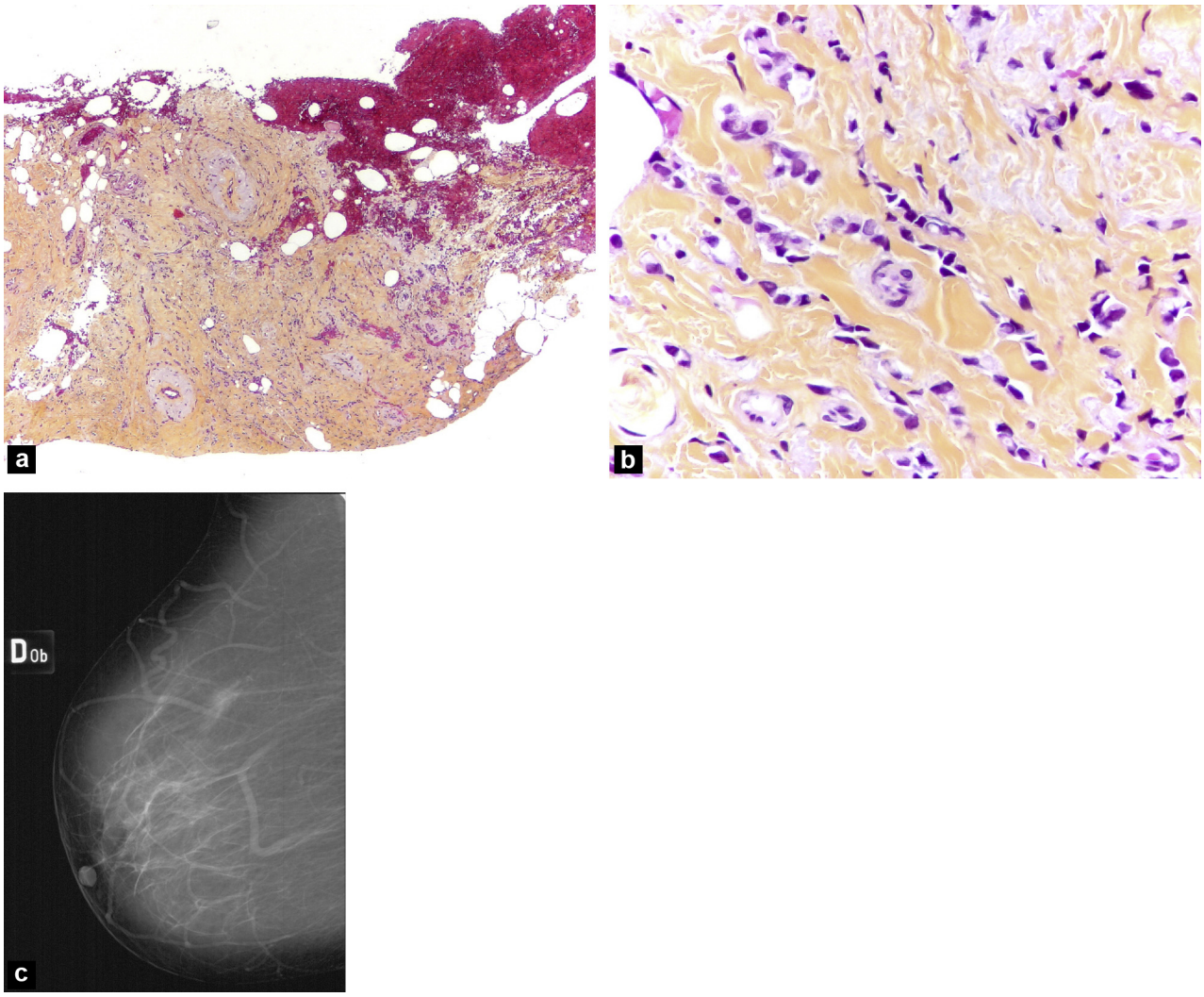

Figure 2. Infiltrating lobular carcinoma. a: microbiopsy under sonography: infiltration of the fat tissue by isolated cells without fibrous stroma reaction; b: HES × 160. Arrangement of cells in ''Indian file''; c: mammogram, right oblique image: focal hyperdensity at the union of the upper quadrants, recently appeared.

The radio-clinical discordance is evocative, between a diffuse cutaneous condition without individualised nodule and a slight translation in mammography: isolated distortion of the architecture (microcalcifications are rare), focal asymmetry of density (Fig. 2c), anomaly often detected on one incidence (cranio-caudal view). The progressive reduction in the size of the breast is rare but evocative with an extensive mass, accounting for the lack of spread of the gland under compression. Harvey compared the tumoral infiltration with a ''spider's web'' [2]. The MRI is the best examination for the detection and measurement of the size of ILC [3].

Mucinous carcinoma

The term is reserved for the pure form (with a very good prognosis) of this carcinoma that accounts for 2% of all infiltrating carcinomas. It consists of large patches of extracellular mucus within which float islands of malignant cells (Fig. 3a).

Classically, it appears in the imaging as a round mass, with a rather circumscribed edge that, in the sonogram, may be mistaken for a cyst with thick contents [4] (Figs. 3b, c). In the MRI, a hyperdense signal in T2 due to the mucinous content of the walls that are enhanced is indicative [5].

Medullary carcinoma

Accounting for 2% of all infiltrating carcinomas, often related to a BRAC1 mutation, this is a carcinoma with distinct outlines consisting of little differentiated cells with a moderate to marked lymphoid infiltrate and little abundant stroma (Fig. 4). In the mammogram, it consists of a very dense round mass with a circumscribed or indistinct edge [2].

Tubular carcinoma

Initially rare (1% of the infiltrating carcinomas), it is becoming more common with the generalisation of screening. It is a

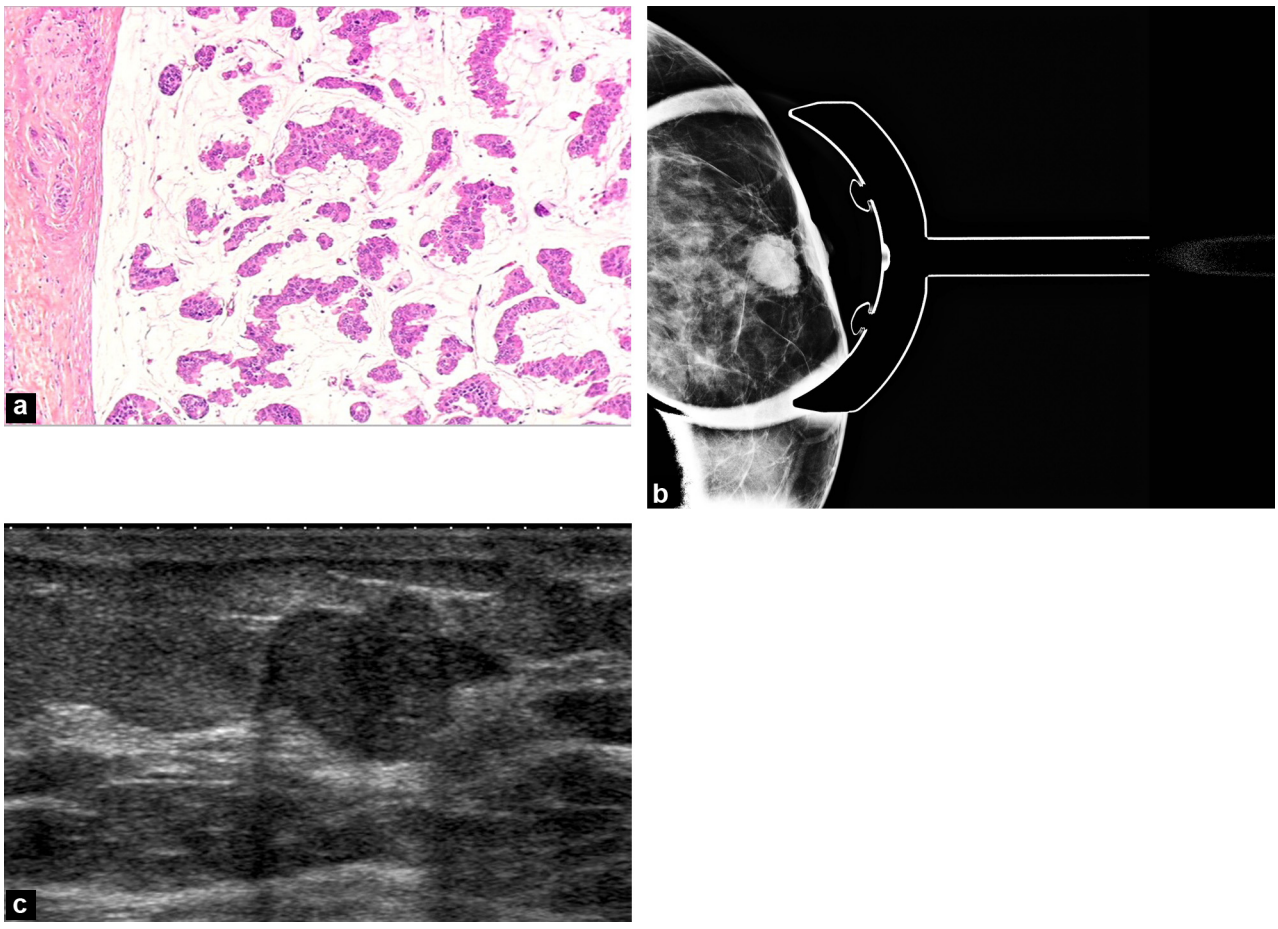

Figure 3. Mucinous cancer. a: HES × 25. Cluster of tumoral cells floating in pools of mucus; b: mammogram, spot compression: oval mass with a slightly microlobulated edge; c: sonogram: mass parallel with microlobulated edge, isoechogenic with posterior enhancement.

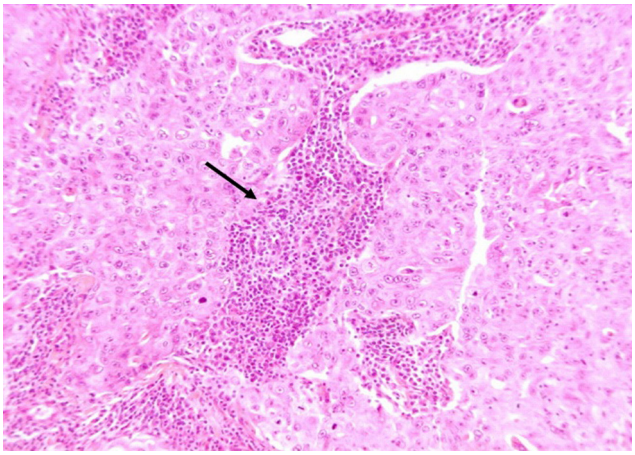

Figure 4. Medullary cancer. HES × 25. Appearance of poorly differentiated grade III infiltrating ductal carcinoma with very high lymphoid infiltrate (arrow).

hard, star-shaped lesion formed by regular cells deposited in tubules, surrounded by an abundant fibrous stroma (Fig. 5a).

The imaging is typically a stellar mass with a very small dense centre or an architectural distortion (Fig. 5b), more rarely a round mass or amorphous microcalcifcations [6].

There are other, rare morphological types: the WHO classification has established 21 of them, some not exceeding a dozen cases described in the literature.

Correlations between the imaging and ''traditional'' prognostic and predictive factors (beginning 2000)

At the beginning of the 2000s, several authors demonstrated that factors such as the tumour grade and the hormone receptors (oestrogens, progesterone) have an influence on the appearance of the imaging [7,8].

The grade

Fairly slow developing grade I tumours (low grade) and grade II tumours (intermediate grade) present a stroma reaction resulting in imaging by spicules and a peri-lesional hyperechogenic halo (Fig. 6a). Grade III (high grade) is the most aggressive and these tumours respond well to chemotherapy. Of rapid evolution, these grade III cancers do not develop a stroma reaction and have a round shape. Shin et al. [8] has shown that the very dense masses with a circumscribed or microlobulated outline, with posterior reinforcement are associated with a high grade and negativity of hormone

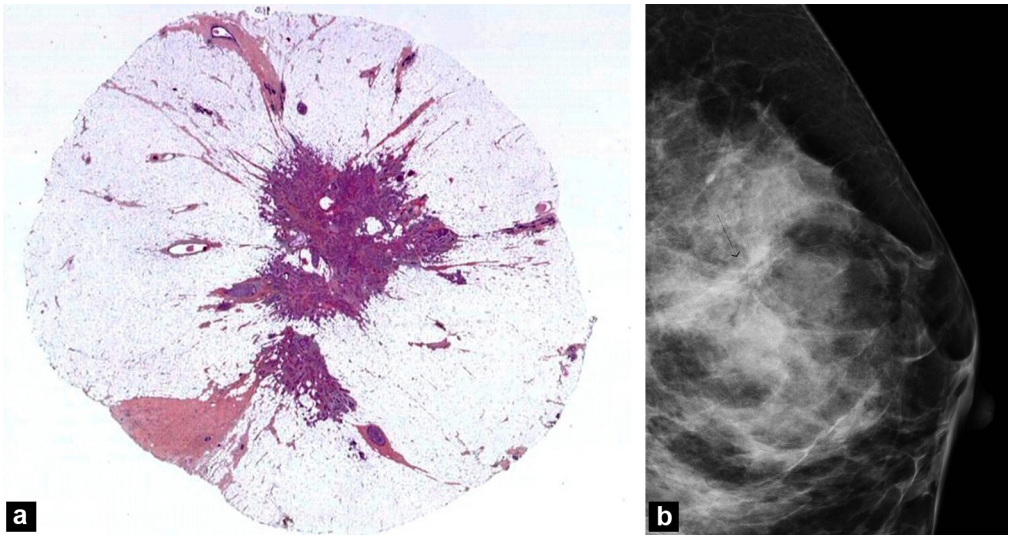

Figure 5. Tubular carcinoma. a: macroscopy: star-shaped, spiculated lesion and infiltration of the peripheral fat; b: mammogram: architectural distortion at the union of the upper quadrants (arrow).

receptors. Vascularisation by colour doppler is generally associated with a high grade [8] (Fig. 6b).

Hormone receptors

The immunohistochemical detection of receptors uses unmasking methods of antigen sites by sensitive antibodies (Fig. 7a). These receptors are detected in the nuclei of infiltrating tumour cells and the neighbouring breast tissue is used as an internal control. The threshold of positivity is generally 10% of the marked cells [9]. The presence of these receptors (RH + tumour) is a good prognosis and indicates a hormone-sensitive tumour. Their absence is a less favourable prognosis. R− tumours respond better to chemotherapy.

In the imaging, R+ cancers often have an irregular shape (80%) and spiculated outlines (68%), significantly more frequent than triple-negative cancers [10] (Fig. 7b). A peripheral echogenic halo is noted in 64% of all R+HER− cancers [11].

Chen et al. compared the MRI appearance of R+ and R− cancers. The most frequent mode of presentation was the mass in both groups. No R+ cancer was presented with a non-mass, observed in 18% of R− tumours. The MRI presentation of R− cancers attests to their aggressiveness: significantly more frequent enhancement with wash-out, greater size and adenopathies [12].

Teifke et al. studied the correlations between the factors of histopathological prognosis comprising the grade and hormone status and the annular enhancement in MRI [13]. There was a significant increase in the peripheral-central-microvessel ratio in grade 3, R− and N+ tumours, accounting for the annular enhancement. According to Teifke, this is the most precise MRI criterion to predict the negativity of hormone receptors, high grade and ganglion invasion [13] (Fig. 7c).

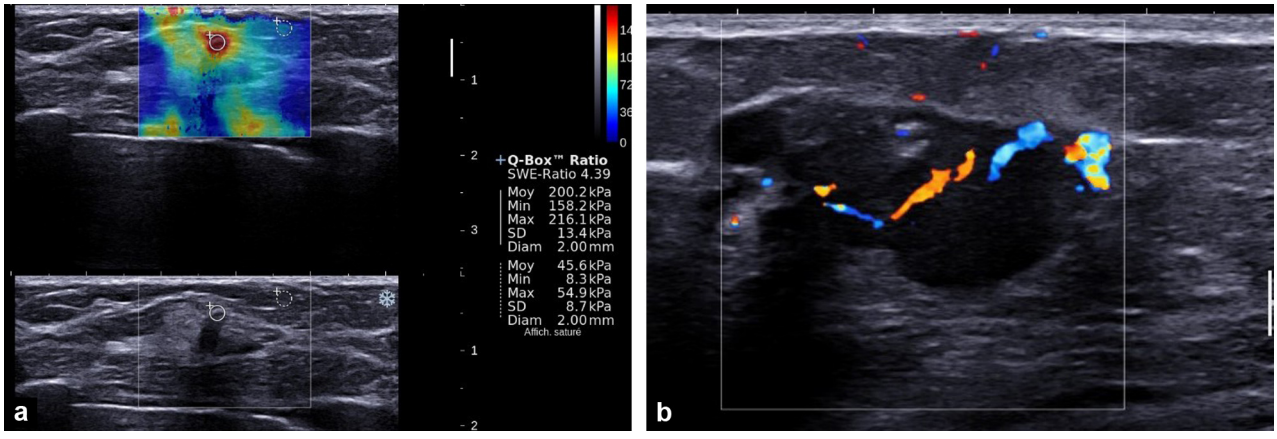

Figure 6. Sonography aspects as a function of the tumour grade. a: infiltrating ductal carcinoma grade I. Sonogram: masse with a centimetric hypoechogenic centre surrounded by a very hard echogenic halo in elastography (200 Kpa), ACR5; b: infiltrating ductal carcinoma grade III. Sonogram: very hypoechogenic, oval mass with a circumscribed edge, with posterior enhancement, vascularized, ACR 4.

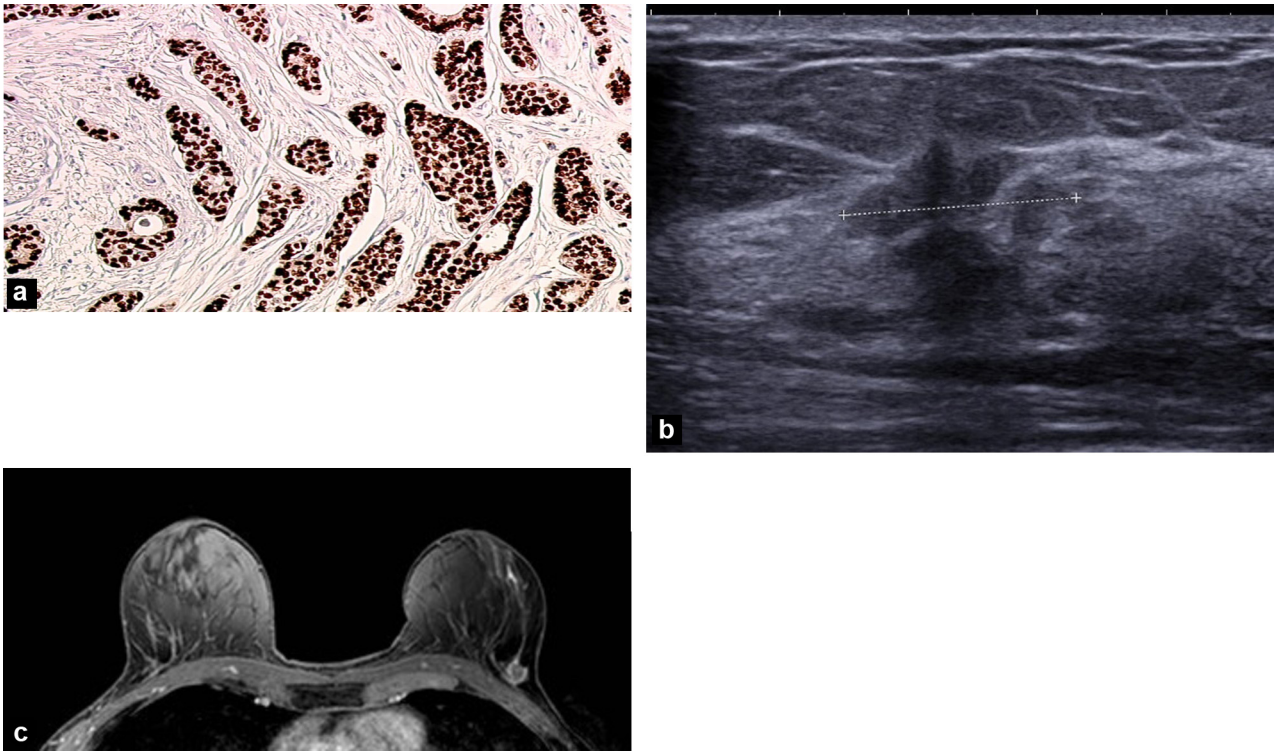

Figure 7. Aspects according to the hormone status. a: immunohistochemistry: infiltrating ductal carcinoma with strong expression of the estrogen receptor in the nuclei of 100% of the tumour cells; b: fifty-five years, infiltrating ductal carcinoma grade I, oestrogen receptors = 90%. Sonogram: hypoechogenic, irregular mass with angular edges; c: forty-three years, left infiltrating ductal carcinoma grade 3, R−, HER2−, N+. MRI after injection: round mass with annular enhancement.

HER2 status

HER2 (or c-erbB2) is a proto-oncogene located on chromosome 17. The amplification or over-expression is observed in 10 to 30% of all cancers. The HER2 status was a factor of a poor prognosis before the introduction of treatment with trastuzumab and is a predictive factor of a response to anti-HER2 therapies. This sub-type of cancer benefits from ''targeted'' therapies, treatments directed against the relatively specific molecular anomalies of cancer cells, here molecules targeting the family of HER2 receptors.

The immunohistochemistry assesses the intensity of the marking and the percentage of cells presenting a circumferential membrane marking attesting to the over-expression of the HER2 membrane protein (Fig. 8a). When the result is equivocal (score 2 +), a complementary study by FISH is requested (in situ fluorescent hybridisation that detects the amplification of the gene) (Fig. 8b).

With the development of the new molecular classification, studies have been carried out on the correlations between imaging and HER2 status.

The new molecular classification (XXIst century)

It was first described by Perou in Nature in 2000, turning an analytical tool based on the morphological type of cancer into an analytical tool based on the analysis of over 40,000 genes. The main molecular types of infiltrating carcinomas are described on the basis of differently expressed genes according to the tumoral type or ''intrinsic signature'' [14].

Luminal A type

It expresses cell proteins located towards the lumen of the ducts, thereby called ''luminal''. It accounts for 50 to 60% of all breast cancers. It is characterized by a high expression of genes of oestrogen receptors (OR), a high expression of genes regulated by OR (*GATA-3*, *FOX A1*, etc.), a low expression of genes related to the proliferation and an absence of over-expression of HER2. *P53* is mutated in 13% of the cases.

As regards the phenotype, in clinical practice, this type corresponds to tubular carcinoma and grade I or II IDC or ILC, expressing oestrogen receptors (R+), with a low index of proliferation (Ki67 < 14%, interpreted in immunohistochemistry technique).

In the mammogram, in the Taneja study, the spiculated mass is significantly more common in the luminal groups (37%) than in the other sub-types [15] (Fig. 9). By sonography, all the criteria of malignancy are often observed: irregular shape, angular or spiculated, echogenic halo, posterior attenuation [16]. The tumour-parenchyma interface attests to the desmoplastic reaction and therefore a fairly slow growth.

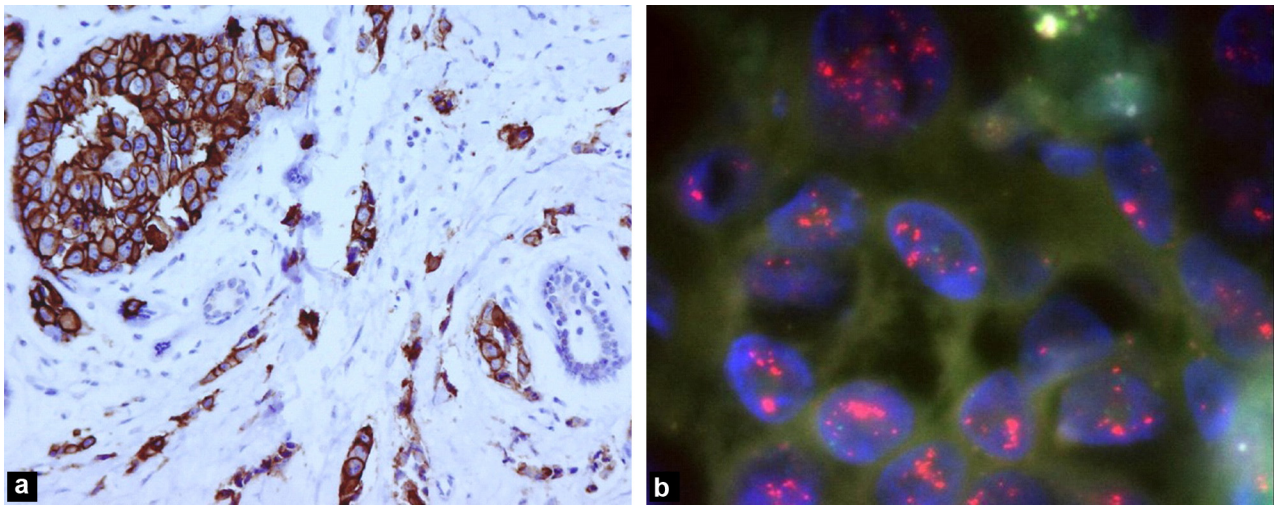

Figure 8. HER2 status. a: immunohistochemistry: circumferential and intense membrane marking attesting to the over-expression of the HER2 membrane protein (Score 3+). Absence of marking of the benign mammary ducts (internal control of specificity). b: FISH (in situ fluorescent hybridization) of the same case showing amplification of gene HER2 represented by two red spots. Formation of clusters of over 10 spots (copies of HER2) by tumor cell nuclei.

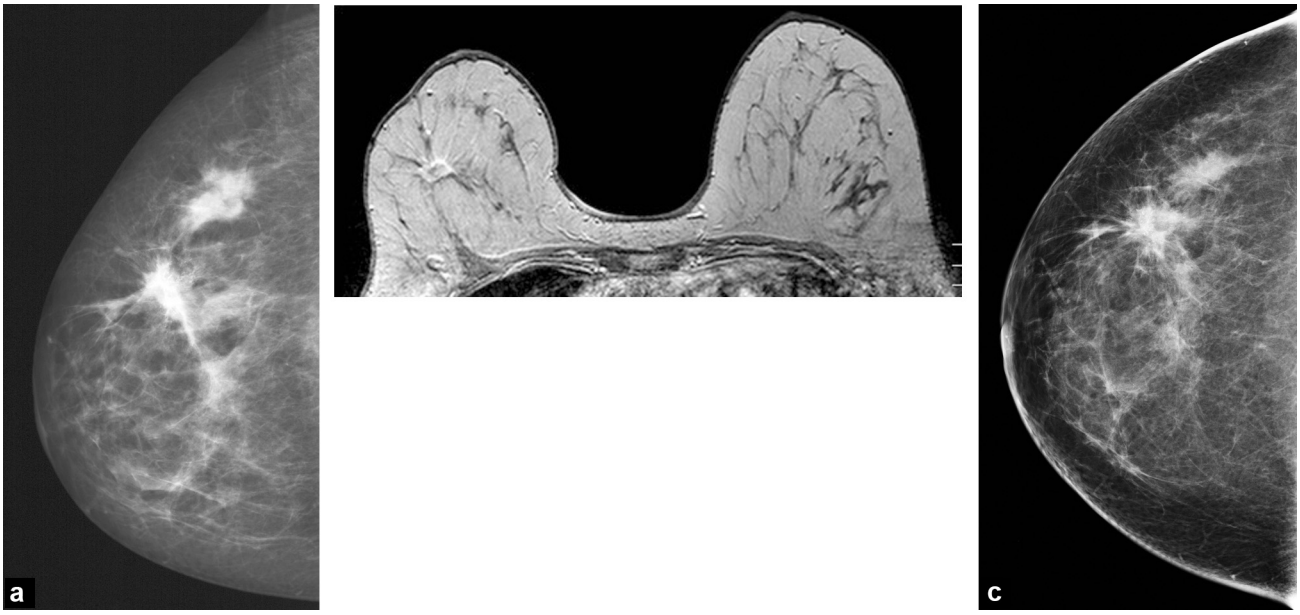

Figure 9. Luminal A sub-type. a: mammogram: spiculated (palpable) mass of 50 mm. Infiltrating ductal carcinoma grade I, oestrogen receptors/progesterone receptors = 90%, Ki67 < 14%, HER2—. b: same patient. MRI after injection: irregular spiculated mass. c: same patient. Mammography control after 4 months of neo-adjuvant hormone therapy: reduction in the size of the mass.

Luminal B type

It accounts for about 20% of all breast cancers. Compared with the luminal A group, it comprises a lower expression of OR genes, a lower expression of OR-regulated genes (*GATA-3*, *FOX A1*, etc.), and a high expression of proliferation-related genes. *P53* is mutated in 66% of the cases.

As regards the phenotype, in clinical practice, this type corresponds to grade II or III infiltrating carcinomas, expressing oestrogen receptors (R+), with Her2 Score 0, 1+, 2+ not amplified, with a high proliferation index (KI67 > 14%) (Fig. 10a). Carcinomas occurring with BRCA 2 mutations often belong to this molecular type.

As noted in the Taneja study, the spiculated mass was more often significantly observed in luminal groups when compared with other sub-types. They occur less often in the luminal B type (27%) than in the luminal A type (37%). Architectural distortion was more often observed in the luminal B type (16%) than in the other sub-types [15]. However, there were only 44 cases of luminal B type in this study. By sonography, Au-Yong observed a statistically significant irregular form (88% of the cases) and posterior attenuation (85% of the cases) [16]. However, the examination was carried out

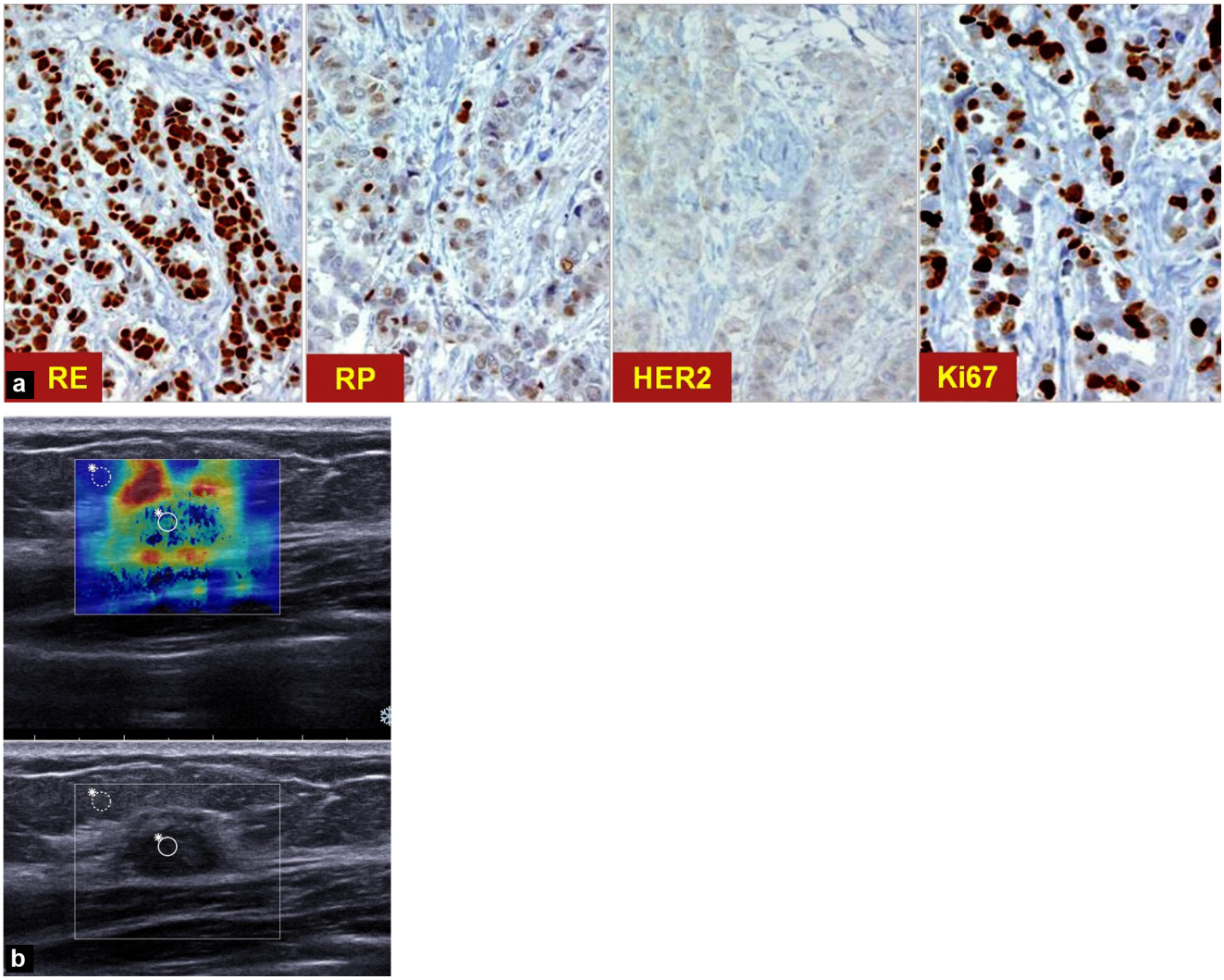

Figure 10. Luminal B sub-type. a: immunohistochemistry: ER = 90%, progesterone receptors = 20%, no over-expression of HER2, Ki67 > 14%. b: sonogram: mass with indistinct edges, moderately hypoechogenic, with a high peri-lesional elastography score. Infiltrating ductal carcinoma grade II, oestrogen receptors = 70% PR = 20%, HER2−, KI67 = 16%. Conservative treatment, adjuvant chemotherapy, hormone therapy.

with a 7.5 mHz probe and the authors acknowledge that they would certainly have obtained different results with more recent equipment (Fig. 10b).

HER2 type

It accounts for 10% of all breast cancers. It is characterized by the absence of OR-related genes, the high expression of genes on the HER2 amplicon (*GRB7*, etc.) and the high expression of proliferation-related genes. *P53* is mutated in 71% of the cases.

As regards the phenotype, in clinical practice, this type corresponds to grade II or II infiltrating carcinomas, not expressing oestrogen (R−) receptors, with Her2 Score 3+ or 2+ in FISH amplified immunohistochemistry, whatever the KI67.

In the imaging, a mass with indistinct outlines is the most common mode of presentation: 42% in the Taneja et al. series [15]. A mass with indistinct outlines is significantly associated with a high grade, a R− status and HER2+ [8]. The presence of calcifications in the mammogram (polymorphous, in the mass or in segmental distribution cluster) is significantly associated with a HER2 + status: their presence may predict a HER2+ status when the HER2 score is equivocally 2+ in the microbiopsy (in immunohistochemistry) [8]. In sonography, a rather irregular mass is observed whose edges are described in different ways in the literature. However, the assessment of the outlines depends on the apparatus and the reading by the operator: significantly indistinct edges in 94% of the masses for Au-Yong et al. [16], but spiculated edges in 56% of the cases by Wang et al. [17]. This author concludes that the spiculated edges help predict the HER2+ status more than the negative receptors [17]. When at the tumour-parenchyma interface, it is more often abrupt in R-HER2+ tumours (91%) than in R+HER2− cancers (64%) [11]. The posterior enhancement is more often observed in R−HER2+ cancers (50%) than in R+HER2− cancers (29%) in the Ko et al. study [11]. Finally, non-masses are most often observed in the HER2+ group: 32% as opposed to 16% of the RE+RP−HER2−, perhaps because the intraductal component is more frequent [8] (Fig. 11).

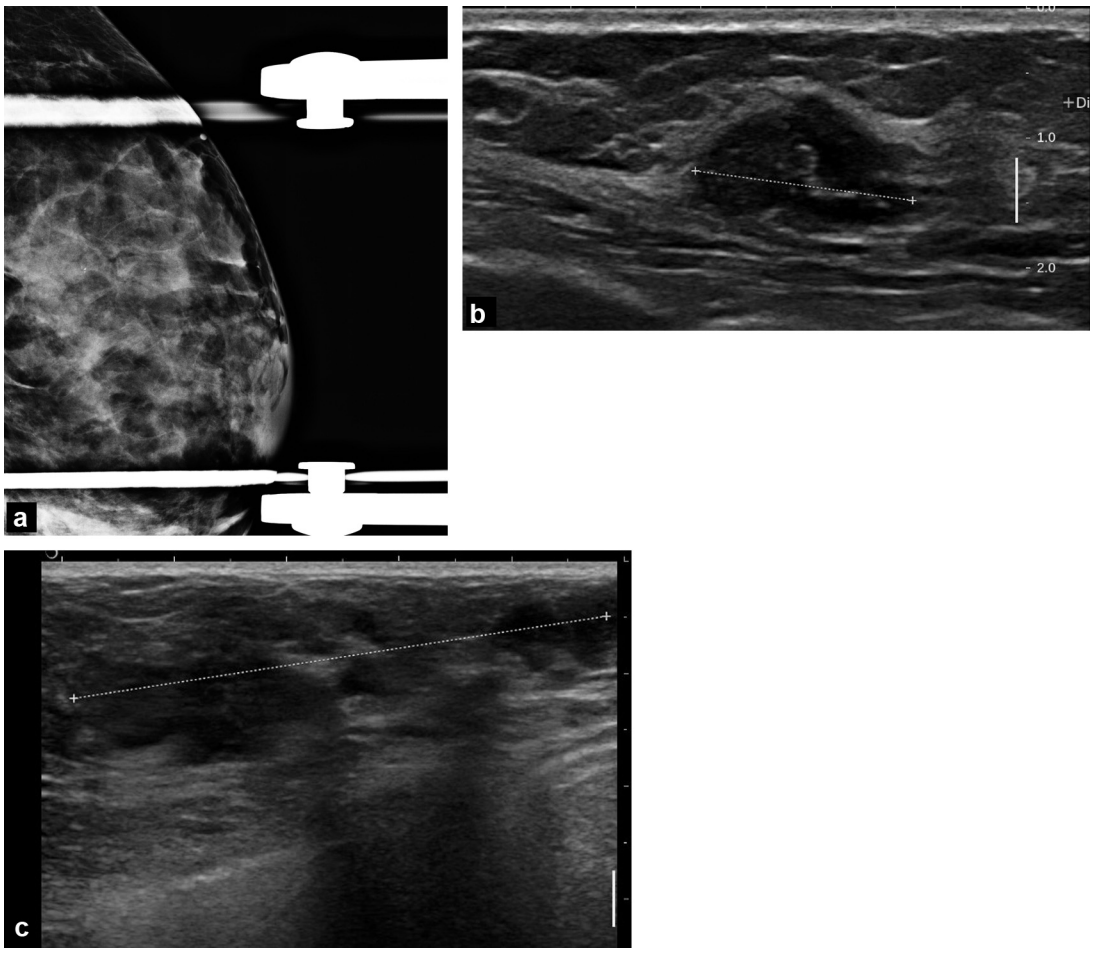

Figure 11. HER2 + sub-types. a: thirty-three years, palpable mass of 6 cm. Mammogram: non-sillhouetted mass, presence of several polymorphous microcalcifications. Infiltrating ductal carcinoma grade II RE-HER2+. Neo-adjuvant chemotherapy and Trastuzumab. b: forty-seven years. Sonogram: 15 mm mass with an abrupt interface. Infiltrating ductal carcinoma RE-HER2+. Conservative treatment, adjuvant chemotherapy and Trastuzumab. c:thirty-six years. Sonogram: ''non-mass'', poorly defined of 5 cm. Infiltrating ductal carcinoma RE-HER2+.

Basal-like type

It accounts for 10% of all breast cancers and 56 to 85% of the triple-negative (TN) cancers [18,19]. It expresses the cytokeratins (CK) of high molecular weight (fibrous intracellular polypeptides) or basal CK (named so because of their expression in the basal or myoepithelial cells of the normal milk ducts). It is characterised by the absence of OR expression, the expression of high molecular weight keratin genes (*CK5*, *CK14*, *CK17*), laminin and FAB7 and the high expression of proliferation-related genes (over-expression of EGFR). A *P53* mutation is observed in 82% of the cases.

In clinical practice, this type corresponds to a determined histological phenotype: grade III IDC, poorly differentiated, R−, HER2−, with lymphocytic infiltrate, zones of tumoral necrosis, fibrotic central zone and ''pushing'' outlines (continuous tumoral flare front, without stroma reaction). It is a heterogeneous group comprising 85% of the BRCA1, medullary and metaplastic cancers.

In the mammogram, Taneja observed fewer spiculated masses (13%) and more masses with a distinct edge (47%) than in the luminal and HER2+ sub-groups [15]. In the sonogram, the halo is significantly less frequent (19%) [16]. Other data is not available in the literature concerning the imaging of the basal-like types.

Triple-negative type

TN cancers account for 7 to 16% of all cancers and 70% of the tumours occurring in BRCA1 mutated women [18,19]. They are characterized by a complete absence of the expression of the oestrogen and progesterone receptor gene and HER2 (''triple negativity'') associated with a high expression of cytokeratin genes of high molecular weight of type 5/6 or 14 and EGFR (epithelial growth factor receptor).

As regards the phenotype, in clinical practice, this type corresponds to grade II or more often III or little differentiated, RE−, HER2− infiltrating carcinomas.

In the mammogram, the mass is the most common presentation, round, oval or lobular in 60 to 75% of the cases, with a circumscribed edge in 24% to 43% of the cases attesting to its rapid growth [11,20–23]. Ko et al. [11] found a significant difference between TN and control groups (OR+PR-HER− and OR+PR-HER+) for the microcalcifications (less frequent since the TN tumour does not go through the precancerous stage) and the focal asymmetries of density (more frequent in the TN). However, the frequency of the

microcalcifications in this sub-type is assessed differently in the literature, more frequent in the series by Boisserie-Lacroix et al. [23]. The rate of normal mammograms is assessed differently, from 0 to 18% [11,20—23]. The negativity of the mammogram may be attributed to the ''masking effect'' of the breast density that reduces the contrast and by the rapid evolution of these tumours that are not accompanied by architectural disorganisation.

In sonography, a predominance of the round-oval-lobular shaped mass is found in 65.1% to 70% [17,23], with an indistinct or microlobulated contour. The tumour-parenchyma interface is more often abrupt in TN tumours (71 to 84%) and HER + tumours (91%) than in R+HER— cancers (64%) [8,11,23]. Very distinct hypoechogenicity is more common: 48% of the cases in Ko et al.'s series [11]. The echostructure may be heterogeneous with zones of necrosis, in five out of 25 cases of tumours over 3 cm in the study by Kojima and Tsunoda [20]. Posterior enhancement is observed in 35.5% to 49% of TN cancers and 50% of R-HER+ cancers [11,23] while it is noted in only 29% of the R+HER2— cancers in the study by Ko et al. [11]. This corroborates Shin et al.'s findings: the posterior enhancement is associated with the high grade and the negativity of the receptors [8]. For Dogan et al., six of the 38 masses (15.8%) had the characteristics of a solid mass of benign appearance [22] (Fig. 12).

In the MRI, the predominance of the presentation of the mass type is observed even more than with conventional imaging: 77.3% to 97% of the cases [22—24]. A T2 hypersignal is noted in almost half of the masses. Dogan et al. attributed this to seats of necrosis although there is not a histological correlation in this study [22]. The existence of a central necrosis is considered to be a factor of a poor prognosis, related to a reduction in the free interval without recurrence, with early metastatic dissemination and an increase

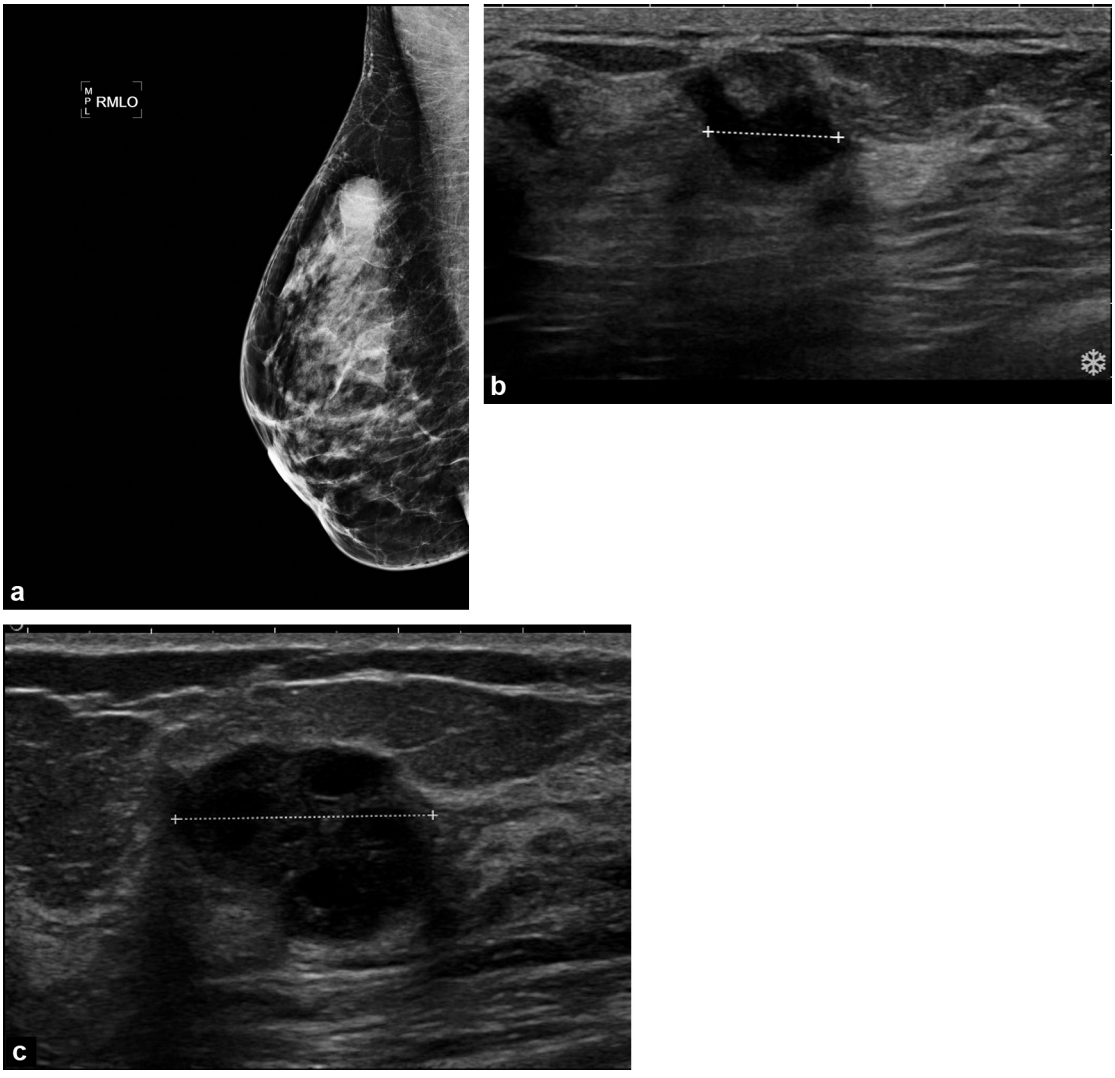

Figure 12. Triple-negative sub-types. a: forty-eight years. Mammogram: round mass at the union of the upper quadrants. Infiltrating ductal carcinoma grade III, oestrogen receptors/progesterone receptors— HER—: conservative treatment, adjuvant chemotherapy. b: fifty-one years. Sonogram: very hypoechogenic 10 mm mass with a circumscribed edge, non vascularized, pseudo-cystic, ACR 4. Infiltrating zf carcinoma grade II, oestrogen receptors/progesterone receptors— HER—. c: forty-two years. Sonogram: 18 mm, oval, very hypoechogenic mass with a circumscribed edge, abrupt interface, with posterior enhancement, ACR4. Infiltrating ductal carcinoma grade III, oestrogen receptors/progesterone receptors— HER—.

in the mortality (whatever the ganglionary status) [25,26]. The morphological criteria for TN cancers in MRI are more suspect than in conventional radiology since the masses have irregular forms in 58.3% of the cases, and an angular edge in 75% of the cases [23] or even spiculated edge in 41.2% of the cases [22] according to the studies. Annular enhancement is often observed, in 76.5% of Dogan et al.'s cases [22] and 80% of Uemastu et al.'s cases [5] although he did not find any in the control group (the comparison was carried out with R+HER− tumours that are rather a good prognosis). The positive predictive value of malignancy is high with this type of enhancement. It is also associated with poor prognostic factors [25]. In the study by Dogan et al., among the 26 masses with annular enhancement, eight also had enhanced internal septa [22]. Finally, as regards the kinetics, a type 3 enhancement curve indicating malignancy (early intense with wash-out) is noted in 91% to 100% of the cases [22,24].

Apocrine type

Its more recent individualisation is still incomplete.

Clinical implications as regards treatment

Breast cancer has become a heterogeneous disease with clinically pertinent sub-groups that have a prognostic impact [14]. In imaging, beyond the characterisation of a mass and its classification in BI-RADS ACR category, it is important, as of the first mammo-sonogram to be familiar with the predictive characteristics of an aggressive tumour sub-type in order to organise the care as quickly as possible for the patient: microbiopsy, which remains indispensable, and appointment with the surgeon/oncologist. In particular, the TN type evolves rapidly and the size of the tumour is higher in young women and should not be confused with a benign tumour by the radiologist.

With infiltrating breast cancer, the indication of adjuvant chemotherapy is based on the analysis of the classic clinicopathological factors and decided on during a meeting involving multidisciplinary agreement based on the recommendations of the consensus conferences (St-Gallen, St-Paul-de-Vence...). At the same time, during the last decade, expression profiles have helped define tumours with a different prognosis, opening the way to therapeutic strategies adapted to the tumour profile, and even to a prediction of the response or non response to chemotherapy.

For example, in patients with a ''good prognosis'', without ganglion invasion, with R+ tumour and grade II (luminal A and B type), the high genome grade (genes associated with the proliferation and regulation of the cell cycle, high Ki67) and the low genome grade now enable the indication for chemotherapy to be validated or rejected.

Genome analysis tests have been commercialised. The price is very high and they are not reimbursed or used in France and are waiting for the conclusions of the therapeutic trials (ex. MINDACT, based on a ''signature with 70 genes'', Mammaprint) carried out to validate the reliability of genome analysis in everyday practice.

Conclusion

We will note the significantly more frequent aspects, based on current knowledge (Diagram 1):

- stellar mammogram-irregular mass with echogenic halo in luminal A sub-type;

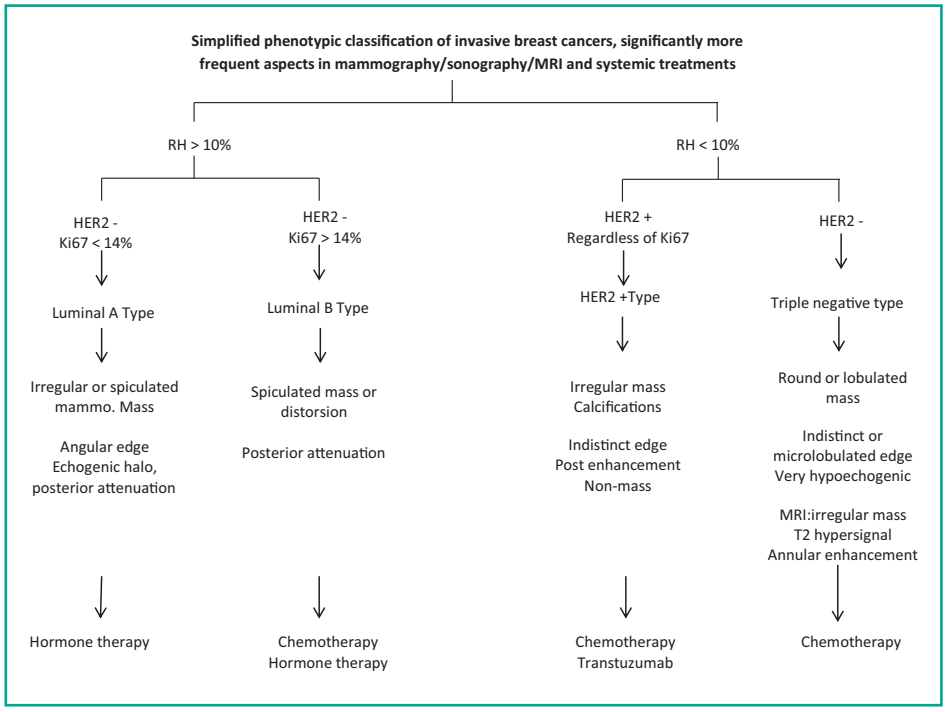

Diagram 1. Simplified phenotypic classification of invasive breast cancers, significantly more frequent aspects in mammography/sonography/MRI and systemic treatments.

- architectural distortion in luminal B sub-type;
- irregular mass with an indistinct edge, with an abrupt interface in the sonogram, or of sonogram non-mass in the HER2 sub-type;
- lobulated mass with an indistinct edge or microlobulated, very hypoechogenic, with an abrupt interface, pseudo-benign, with annular enhancement in the MRI in the triple-negative sub-type.

It is necessary to back up these correlations between the imaging and molecular classification by more statistically powerful studies.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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